

### **REMARKS**

Claims 1, 4, 5, 8, 9, 11 and 17 have been amended in this response. Claim 1 has been amended to indicate that the method includes “separately administering to the mammal at least one mRNA which codes for GM-CSF.” Support for the amendment to claim 1 can be found, for example at page 1, first paragraph. Claim 4 has been amended to refer to “the” method of claim 1 as opposed to “a” method of claim 1. Claims 1 and 5 have been amended for clarity by deleting the phrase “containing a region” in the claims. Claims 8 and 9 have been amended to delete the phrase “in the form of” in the claims. Claim 17 has been amended to indicate that the “pathogen is a protozoological, viral and/or bacterial infection.” The amendments to claims 1, 4, 5, 8, 9, 11 and 17 are fully supported by the specification and claims as originally presented. Claims 21-27 have been added and are supported by the specification e.g., in paragraph 1 on pages 9 and 15. No new matter is added by these amendments and entry thereof is respectfully requested.

Claim 6 has been cancelled herein and claims 18-20 have been previously cancelled. Upon entry of this amendment, claims 1-5, 6-17 and 21 would be pending.

Applicants address herein each issue raised in the Office Action of May 12, 2010.

#### **1. Claim Objections**

##### **Claim 1**

Claim 1 is objected to because “[i]t is not clear how the preamble and conclusory steps are related i.e., if the steps that intensify or modulate an immune response are responsible for the method of immunostimulation.” In response, Applicants have amended the preamble of claim 1 to indicate that the method is for “stimulating an immune response in a mammal” and have deleted the recitation “whereby an immune response in the mammal is intensified or modulated.” Thus, the objection to claim 1 has been obviated. Accordingly, withdrawal of the objection to claim 1 is respectfully requested.

##### **Claims 7 and 21**

The Office Action indicates that “[c]laim 7 should be amended to include the article ‘a’ prior to polycationic and thereafter claim 21 should use a ‘the’.” Applicants respectfully disagree and assert that the alternative language of claim 7 and claim 21 is proper.

In particular, claim 7 indicates that the “the at least one mRNA from step (a) and/or from step (b) is complexed or condensed with at least one cationic or polycationic agent” and claim 21 indicates “the cationic or polycationic agent.” As stated in the M.P.E.P., “[a]lternative expressions using ‘or’ are acceptable, such as ‘wherein A, B, C, or D’ and such expressions were found to not violated 35 U.S.C. 112, second paragraph. *See* M.P.E.P § 2173.05(h)II. Thus, Applicants assert that the omission of “a” prior to “polycationic agent” in claim 7 and the omission of “the” prior to polycationic agent” in claim 21 is proper and amendment to the claims is not required. Accordingly, withdrawal of the objection to claim 7 and claim 21 is respectfully requested.

#### Claim 1

The Office Action indicates that in order to clarify that the “molecule encoding the antigen is mRNA and not some other molecule accompanying the RNA that is administered” claim 1 should be amended to recite “-- at least one mRNA which codes for --.” In response, ~~claim 1 has been amended herein to indicate that the “at least one mRNA...codes for at least one antigen.”~~ Accordingly, Applicants Amendment herein to claim 1 has obviated the objection and withdrawal of the objection to claim 1 is respectfully requested.

#### Claim 5

The Office Action indicates that “Claim 5 for simplicity should be amended to recite -- wherein the mRNA which codes for at least one antigen-- as the claim already states that the mRNA contains the coding region.” Office Action at page 3, third full paragraph. In response, claim 5 has been amended herein to recite the suggested language. Accordingly, withdrawal of the objection to claim 5 is respectfully requested.

#### Claim 2

The Office Action indicates that “[c]laims 1 and 2 have amended the presentation of a. and b. to (a) and (b) except in line 1 of the claim 2. It would be remedial for consistency to amend this occurrence.” Office Action at page 3, last full paragraph. In response, Applicants note that claim 2 was amended in the response to the Office Action mailed August 11, 2009 to

replace “step b.” with “step (b).” Thus, this objection is rendered moot as reflected in claim 2 as presented herein. Accordingly, withdrawal of the objection to claim 2 is respectfully requested.

#### Claims 5 and 6

The Office Action also objects to claims 5 alleging that it is improper to recite in the alternative “matrix M1 protein or influenza B matrix” in the claim as the “Markush group language establishes a group wherein the proteins are not listed in the alternative.” Office Action at page 3, last full paragraph. The Office Actions indicates that “[i]t would be remedial to omit the language ‘in particular’ and ‘or’ and include these two proteins within the listing” in claim 5 and that a “[s]imilar amendment to claim 6 is required.” Id. In response, claims 5 has been amended herein to omit the recitation of “in particular” and “or” and claim 6 has been cancelled. Accordingly, withdrawal of the objection to claims 5 and 6 is respectfully requested.

#### Claim 4

The Office Action objects to claim 4 alleging that “it is improper to use the article ‘a’ when referring to the method of claim 1.” Office Action, paragraph bridging pages 3-4. In response, claim 4 has been amended to replace “a” with “the” in referring to the method of claim 1. Accordingly, withdrawal of the objection to claim 4 is respectfully requested.

## **2. Rejections under 35 U.S.C. § 112, Second Paragraph – Indefiniteness**

#### Claim 5

The Office Action alleges that claim 5 is indefinite because “the phrase ‘for example’ renders the claim indefinite because it is unclear whether the limitation(s) following the phrase are part of the claimed invention.” Office Action at page 4, third full paragraph. Claim 5 has been amended herein to delete the use of “e.g.” from claim 5. Accordingly, withdrawal of the rejection of claim 5 under 35 U.S.C. §112, second paragraph is respectfully requested.

#### Claims 8 and 9

The Office Action has rejected claims 8 and 9 under 35 U.S.C. §112, second paragraph because allegedly the use of the term form “does not reflect that it is actually i.e. UTR stabilized mRNA.” Office Action at page 4, penultimate paragraph. As a result, Claims 8 and 9 have been amended herein to delete the phrase “in the form of.” Accordingly, withdrawal of the rejection of claims 8 and 9 under 35 U.S.C. §112, second paragraph is respectfully requested.

Claims 10-15

The Office Action has rejected claims 10-15 alleging that there is insufficient antecedent basis for the limitation “the modified mRNA” and/or “the wild-type RNA” in reference to claim 1. The Office Action thus alleges that, “for purposes of art, these claims will be considered to be dependent on claim 9.” In response, Applicants assert that claims 10-15 were amended in the response to the Office Action mailed August 11, 2009 to depend from claim 9. The listings of claims as provided herein reflect the prior amendment to claims 10-15 and thus the rejection of these claims under 35 U.S.C. §112, second paragraph is rendered moot. Accordingly, withdrawal of the rejection of claims 10-15 is respectfully requested.

Claim 17

Claim 17 is rejected in the Office Action under 35 U.S.C. §112, second paragraph as allegedly “being incomplete for omitting essential steps, such omission amounting to a gap between the steps.” Office Action at page 5, first paragraph. The Office Action indicates that the “omitted steps are what the connection between the treatment and the immunostimulation are.” Id. In response, Applicants assert that claim 17 has been amended herein, to indicate that the “pathogen is a protozoological, viral and/or bacterial infection.” Thus, Applicants have deleted the steps in the claim directed to treatment and immunostimulation. Accordingly, the rejection of claim 17 has been rendered moot and withdrawal of the rejection of claims 17 is respectfully requested.

Claim 6

The Office Action has rejected claim 6 under 35 U.S.C. §112, second paragraph as allegedly lacking antecedent basis for the limitation of “the at least one mRNA encoding a cytokine” in claim 1. Office Action at page 5, second paragraph. Applicants note that claim 6 has been cancelled herein and thus the rejection of claim 6 under 35 U.S.C. §112, second paragraph has been rendered moot.

- 3. The Rejection under 35 U.S.C. §103(a) over Terman (US 20050112141) in view of Horton (US Patent No. 7,268,120) and Cannon and Weissman (DNA and Cell Biology, 2002, pgs. 953-961) should be withdrawn**

Claims 1-3, 5-9 and 12-17 are rejected under 35 U.S.C. 103(a) as allegedly obvious over Terman et al (US 20050112141) (hereinafter “Terman”) in view of Horton et al (US Patent

7,268,120) (hereinafter “Horton”) and Cannon and Weissman (DNA and Cell Biology, 2002, pages 953-961).

The Office alleges that Terman demonstrates the use of tumor antigen nucleic acid with either a cytokine or CpG or adjuvant RNA to enhance the immune response. Office Action at page 6, second paragraph. The Office further alleges that Terman teach that Sag transfected cells are activated by cytokine treatment and that CpG DNA is also introduced into the cell. *Id.* Finally, the Office alleges that Terman teaches that Sag nucleic acid addition can be considered an adjuvant RNA as Terman allegedly teaches that a nucleic acid can be a DNA or RNA. *Id.*

The Office acknowledges that “Terman et al do not teach that the antigen mRNA is administered followed by administration of cytokine mRNA.” Office Action at page 7, first full paragraph (emphasis added). Nonetheless, the Office alleges that “Terman et al do teach that the antigen mRNA is administered followed by administration of cytokines” and that “the art teaches that cytokine mRNA is administered as a preferential way to treat cancer.” *Id.* at last paragraph. More specifically, the Office alleges that Cannon and Weismann teach:

Advantages of DNA vaccines apply to RNA vaccines while many of the problems do not. Antigen encoding mRNAs can be delivered as a mixture to provide multiple pathogen epitopes and they can also be mixed with mRNAs encoding immune system modulating proteins such as cytokines to improve the immunogenicity or direct the type of response, as has been done with some DNA vaccine candidates (Leitner et al., Prayaga et al., 1997; Chow et al., 1998)...

and that “[g]iven these teachings it would have been obvious to one of ordinary skill in the art at the time the invention was made to use cytokine mRNA in the treatment protocol of Terman et al because Terman et al teach that it is within the ordinary skill of the art to use tumor antigenic mRNA to modulate immune responses followed by cytokine treatment and because Horton et al teach that it is within the ordinary skill of the art to use cytokine mRNA for treatment protocols directed to similar methods as those of Terman et al.” Office action at page 8, first paragraph. Finally, the Office concludes that “[b]ased upon the teachings of the cited references, the high skill of one of ordinary skill in the art, and absent evidence to the contrary, there would have been a reasonable expectation of success to result in the claimed invention.” *Id.* at page 9, first paragraph.

Applicants respectfully disagree with the Office’s characterizations and conclusions, and traverse as follows:

- A person of skill in the art would not have been motivated to combine Terman with Horton and Cannon and Weissman in developing the claimed methods of stimulating an immune response because Terman teaches away from the *separate* administration of two different mRNAs;
- A person of skill in the art would not have provided a reasonable expectation that the asserted combination could produce a successful method of stimulating an immune response by separately administering of two different mRNAs; and
- A person of skill in the art would have deemed the administration of an mRNA which encodes an antigen and separately administering an mRNA which encodes for GM-CSF to have provided unexpectedly superior benefits over what could have been expected the cited art.

The currently pending claims are directed at methods of stimulating an immune response in a mammal having a pathogen or tumour comprising the steps of administering to the mammal at least one mRNA which codes for at least one antigen of a pathogen or codes for at least one tumour antigen and *separately* administering to the mammal at least one mRNA which codes for GM-CSF.

#### **I. Terman Teaches Away from the Claimed Methods**

Terman discloses the integration of immunostimulatory sequences (“ISS”), e.g. coding for cytokines, into an antitumor DNA sequence. *See* paragraphs 0164 and 0164. However, Terman neither discloses the use of mRNA for administration of the antitumor antigen nor an mRNA encoding a cytokine in general and GM-CSF in particular. Moreover, even though paragraph [0376] of Terman refers to administration of tumor specific mRNA, it does not disclose the separate administration of at least one mRNA which codes for at least one antigen of a pathogen or a tumor and at least one mRNA which codes for GM-CSF. Consequently, even when relying on the generic statement by Terman in paragraph [0049], which states that nucleic acid molecules or separate nucleic acid molecules may also code for cytokines (amongst a multitude of alternatives), the skilled artisan would not have derived the present invention as presently claimed.

Terman teaches the insertion of ISS into nucleic acid sequences of SAgS and tumor associated antigens and administration of the same for transfecting tumor cells, antigen presenting cells and accessory cells including muscles cells in vitro or in vivo. Terman, therefore, provides for multicistronic nucleic acid molecules. Accordingly, the methods taught in Terman necessarily require *simultaneous administration* of all components encoded by the

nucleic acid sequence encoding different peptides in *one* single step. Terman, therefore, *teaches away* from the presently claimed invention which requires *separate* administration of mRNA. Applicants note that the specification and examples provided in Terman fail to show a separate administration of nucleic acid sequences encoding different peptides but instead provide, for example, the administration of a formulation containing mRNA coding for the SAg/tumor associated antigen protein into the tail vein of mice. *See* Terman at paragraph [1258]. Consequently, it is improper to combine references in the context of a § 103 rejection, where the references teach away from their combination. *In re Grasselli*, 713 F.2d 731, 743, 218 USPQ 769, 779 (Fed. Cir. 1983); MPEP 2145.

**2. The Cited References would not have provided a reasonable expectation that a successful method of stimulating an immune response by separately administering of two different mRNAs could be achieved**

Even if a person of skill in the art would have combined Terman, Horton, and Cannon and Weissman in the manner asserted in the Office Act (which applicants contest), the combination still fails to provide a reasonable expectation that the claimed methods would succeed in stimulating an immune response in general and a Th1 response in particular. The Federal Circuit has held that “[o]bviousness does not require absolute predictability of success . . . all that is required is a reasonable expectation of success.” *In re Kubin*, 2008-1184, (Fed. Cir. 2009) citing *In re O’Farrell*, 853 F.2d 894, 903 (Fed. Cir. 1988). As such, even though an invention may be “obvious to try,” it nevertheless remains patentable if the cited prior art combination fails to provide one of skill in the art (at the time of filing of the relevant application) with “a reasonable expectation of success.”

Specifically, Terman fails to teach the necessary steps to overcome the known disadvantages for RNA or mRNA vaccines in the art as of the priority date of the present application. In particular, as discussed in the present specification, a significant disadvantage of the mRNA vaccines generally known in the prior art is that only a humoral immune response (Th2 type) is triggered by an mRNA vaccination. *See* specification at page 4, last paragraph. However, because all viruses and numerous bacteria penetrate into cells where they are protected from antibodies, it is necessary to trigger a cellular immune response (Th1 type) in order to elicit an antitumor or antiviral immune response.

Applicants presently claimed method of separately administering at least one mRNA which codes for at least one antigen of a pathogen or codes for at least one tumour antigen and separately administering to the mammal at least one mRNA which codes for GM-CSF results in

a significant increase of the IFN-gamma secretion and furthermore a significantly improved Th1-response. Due to the strong and significant increase of the IFN-gamma-secretion, an immunostimulatory effect is triggered when the cytokine, preferably GM-CSF, is administered approximately 24 hours after administration of the mRNA according to step (a) of the present claims. *See* results shown in Figure 5 (RNA GM-CSF t+1) and the experiment described in Example 7. Such an effect could not be predicted by a person of skill in the art even if they had retrospectively assembled the discrete passages set forth in the Office Action.

**3. The separate administration of an mRNA which encodes an antigen and an mRNA which encodes for GM-CSF provide unexpectedly superior results**

Again, as opposed to Terman, which as stated above suggests the *simultaneous administration* of all components encoded by the nucleic acid sequence in one single step, Applicants discovered that separately administering an mRNA encoding for an antigen of a pathogen or tumor and an mRNA encoding for GM-CSF provides a significantly enhanced immunostimulatory response.

Applicants surprisingly discovered that separate administration of compounds according to the claimed methods exhibit particular advantages over any of the administration modes of the prior art and in particular over Terman. Whereas Terman discusses *ex vivo* treatment of accessory cells, such as DCs, by proteins such as GM-CSF, as a basic requirement for initiation of an immune response, the presently claimed methods allow a specific and stronger immune response over that which would be obtained by any of the methods as shown in Terman when administering an mRNA encoding an antigen of a pathogen or at least one tumor antigen and then separately administering a GM-CSF mRNA. These are results that could not have been reasonably expected by one of ordinary skill in the art at the time of filing.

Accordingly, the methods of the present invention unexpectedly boost the immune response to a significantly higher level and, additionally, unexpectedly shift the immune response from a Th2 immune response to a Th1 immune response. These unexpected effects are extremely beneficial and provide significant advantages over the prior art methods when carrying out an antitumor treatment or when administering a vaccine against a pathological agent.

As discussed herein above, Terman fails to teach or suggest the method as presently claimed involving separate administration of an antigen encoding mRNA and a GM-CSF encoding mRNA. Moreover, the presently amended claims provide for the possibility of

administering both components, i.e., an mRNA encoding an antigen from a pathogen or at least one tumor antigen and separately administering a GM-CSF encoding mRNA, at different injection sites, at different times and using different administration modes. For example, an injection with the component used according to step (a) may occur systemically, whereas an injection with the component according to step (b) may occur directly into one or more tumor sites. Furthermore, a local injection may occur at the same injection site at different times. Wherein the injection of a component according to step (a) at a specific injection site already results in a significant immunological reaction at this specific site, a separate administration site may be selected for the component according to step (b) to avoid irritation at the first administration site. Additionally, administration of both components according to steps (a) and (b) in the form of an mRNA (i.e., not as a protein or a multicistronic nucleic acid) significantly increases the length of the Th1 immune response without exhibiting the severe side effects of a DNA vaccination, which may occur when carrying out the methods taught by Terman. Consequently, this may result in a reduction in the number injections required.

Horton fails to make up for the deficiencies described above. Although Horton discloses on page 13, last paragraph, that the polynucleotide sequence encoding one or more cytokines may be RNA or an mRNA, it neither suggests a combination of two different mRNAs nor the separate administration of mRNAs as included in the present method claims. Thus, nothing in Horton would teach or suggest to a person of ordinary skill in the art the administration of at least one mRNA which codes for at least one antigen of a pathogen or codes for at least one tumour antigen and *separately administering* to the mammal at least one mRNA which codes for GM-CSF.

Cannon and Weissman also fail to bridge the aforementioned deficiencies. Cannon and Weissman disclose that antigen encoding mRNAs can be delivered as a mixture to provide multiple pathogen epitopes and that they can also be mixed with mRNAs encoding immune system modulating "proteins such as cytokines to improve immunogenicity or direct the type of response..." See Cannon and Weissman, page 955, left column, second paragraph. As such, the mixture described in Cannon and Weissman requires the simultaneous administration of all components. Thus, Cannon and Weissman do not teach or suggest the separate administration of the components of the mixture or the use of a GM-CSF encoding mRNA, which – beyond separate administration – provides a particularly advantageous effect. Accordingly, nothing in

Cannon and Weissman would teach a person of ordinary skill in the art the separate administration of at least one mRNA which codes for at least one antigen of a pathogen or codes for at least one tumor antigen and separately administering to the mammal at least one mRNA which codes for GM-CSF.

Applicants respectfully request withdrawal of the current rejection of claims 1-3, 5-9 and 12-17 under 35 U.S.C. 103(a) as allegedly obvious over Terman, Horton and Cannon and Weissman.

**4. The Rejection of Claims 1-17 and 21 under 35 U.S.C. §103(a) over Terman (US 20050112141) in view of Horton (US Patent No. 7,268,120) and Cannon and Weissman (DNA and Cell Biology, 2002, pgs. 953-961) further in view of Draghia-Akli (US Patent No. 7,316,925) or Weiner et al (US 20020123099) should be withdrawn**

Claims 1-17 and 21 are rejected under 35 U.S.C 103(a) as allegedly obvious over Terman, Horton, and Cannon and Weissman as applied to claims 1-3, 5-9 and 12-17 above, and further in view of Draghia-Akli (US Patent No. 7,316,925) (“Draghia-Akli”) or Weiner et al (US 20020123099) (“Weiner”). The Office alleges that the combination of Terman, Horton and Cannon and Weissman teach a method for immunostimulation in a mammal by administration of at least one mRNA encoding at least one antigen of a tumor in combination with a cytokine or CpG.

However, the Office acknowledges that the combination of Terman, Horton, and Cannon and Weissman do not teach an mRNA which has been modified by increased GC content or increased AU content in the ribosome binding sequence nor is the cationic or polycationic agent listed as protamine or poly-L-lysine or histones. Office Action at page 9, last paragraph. Accordingly, the Office relies on Draghia-Akli or Weiner for disclosing modified mRNA to increase stability.

As discussed herein above in response to the obviousness rejection over claims 1-3, 5-9, and 12-17, Terman, Horton and Cannon and Weissman fail to teach the separate administration of at least one mRNA which codes for at least one antigen of a pathogen or codes for at least one tumor antigen and separately administering to the mammal at least one mRNA which codes for GM-CSF. Neither Draghia-Akli nor Weiner make up for the deficiencies of these references.

As indicated by the Office, Draghia-Akli teach “that a bias of GC content can increase mRNA stability” and that Weiner teach “that the environment of the ribosome binding site is

improved by an AT rich sequence.” Office Action at page 10, second and third paragraphs. However, nothing in Draghia-Akli nor Weiner teach or suggests the separate administration of mRNA to stimulate an immune response.

In view of the foregoing remarks, Applicants respectfully request reconsideration and withdrawal of the rejection of claims 1-17 and 21 under 35 U.S.C 103(a).


## 5. Conclusion

In view of the foregoing amendments and remarks, Applicant respectfully requests reconsideration and reexamination of this application and the timely allowance of the pending claims. The Examiner is invited to telephone the undersigned if that would be helpful to resolving any issues.

It is believed that no fees are due; however, the commissioner is authorized to charge any fees and credit any overpayments to Deposit Account No. 50-5071. Additionally, please grant any extensions of time required to enter this response and charge any additional required fees to our deposit account 50-5071.

Respectfully submitted,

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